

or neonatal deaths, and, if possible, on all women who are pregnant or contemplate pregnancy; also on all persons, male or female, who are to have repeated transfusions.

2. Every community should have access to a panel of donors belonging to each of the four blood groups whose erythrocytes lack the Rh antigen (Rh—).

3. Blood counts and differential smears should be made from the cord blood of all newborn babies in order to be on the alert for the existence of erythroblastosis neonatorum.

Post and Scott streets.

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EXOPHTHALMOS IN DISEASES OF THE THYROID*

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SINCE the first description of hyperthyroidism by Parry,¹ exophthalmos has been considered an integral part of this syndrome. Seventy-five years ago, Von Graefe² drew attention to the eye signs and discussed many of the factors in exophthalmos that all too often have escaped subsequent notice.

Stare, characterized anatomically by retraction of the upper lids and exposure of the sclerae above the iris, is frequently misinterpreted as exophthalmos. A staring expression is more commonly seen in exophthalmic goiter than is measurable protrusion of the eyeballs and generally disappears following adequate treatment of the hyperthyroidism.^{3,4} It can be distinguished from true exophthalmos by having the patient close his eyes gently so that the actual prominence of the globes can be estimated by scrutiny of the eyes from both the anterior and lateral aspects.

True exophthalmos, on the other hand, is associated with a number of subjective and objective phenomena that aid in a more or less precise estimate of its presence. The eyes usually have both a staring and uncomfortably prominent appearance. Lacrimation is often excessive and the conjunctivae may be injected; this also may be reflected subjectively by local irritation and discomfort. Patients not infrequently complain of a sense of pressure behind the eyes and less often of frontal headaches of varying severity. Palpation reveals increased orbital resistance due to increased volume of the postglobal tissues of the orbit. More of the

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sclera above the iris is exposed and the eyes appear to bulge forward and downward so that more of the sclera below the iris shows than is usual in normal persons. Periorbital edema is common and is characterized by local swelling of both eyelids. As pointed out by H. C. Naffziger,⁵ a finger-like area of edema of the upper lid, widest at the nasal end, is present when this periorbital edema is of severe degree. Edema of the sclera is seen only with severe exophthalmos and considerably alters the prognosis, as far as the eyes are concerned, since so many in this group will eventually need supra-orbital decompression.⁵ Unilateral exophthalmos is rare, whereas a greater degree of exophthalmos on one side than on the other is not uncommon. A wider palpebral fissure on one side should not be confused with unilateral exophthalmos. Lid lag is found with or without exophthalmos, but is more common and usually more accentuated when the latter is present. Impaired convergence may result from a number of causes, among which is weakness of one or both internal rectus muscles resulting from edema and cellular infiltration of the extraocular muscles in exophthalmic goiter. These same tissue changes cause diplopia when they are extensive. In brief summary, many, and even all, of the symptoms and signs enumerated occur with significant exophthalmos and should lead to an accurate clinical estimate. In turn, this accurate clinical estimate will be important in the instances of severe exophthalmos, since the patient then will

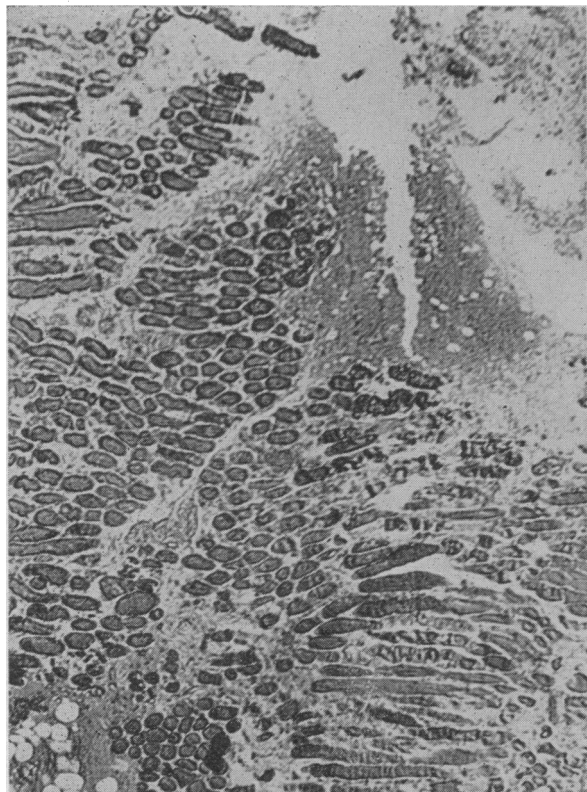


Fig. 1.—Photomicrograph (X60) of extraocular muscles of a patient with severe, progressive exophthalmos; biopsy during supraorbital decompression. There is marked edema of the interstitial tissues and of muscle fibers. Cellular infiltration was present, but does not show clearly in the photomicrograph.

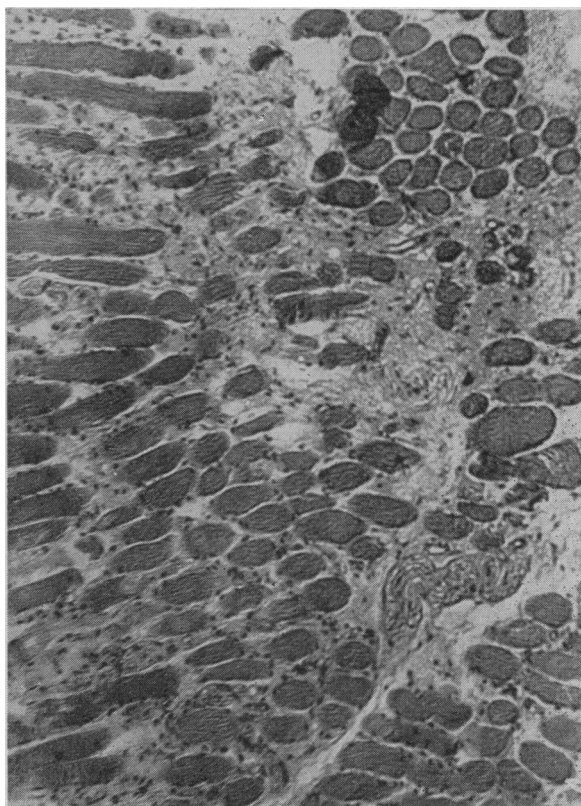


Fig. 2.—High-power photomicrograph (X120) of a section of muscle from the same section shown in Plate 1.

be followed more carefully and appropriate treatment directed to the eyes *per se*.

ETIOLOGY

The cause of exophthalmos in hyperthyroidism in man now has been adequately explained by (1) edema, cellular infiltration, late fibrosis of the extraocular muscles (Figures 1 and 2), and (2) edema of other tissues of the posterior orbit.^{5,6} These tissue changes are not due to hyperthyroidism directly; indeed, they are seen in the extreme after the hyperthyroidism has been treated and hypothyroidism perhaps has followed. Sympathetic stimulation is no longer thought to play a part.⁷ Marine,⁸ Smelser,⁹ Aird,¹⁰ and others, believe that the tropic hormones of the anterior pituitary, particularly the thyrotropic, may be secreted in excess and may be responsible for the tissue changes found in experimental animals and in man.* These tissue changes, particularly of muscles, occur elsewhere in the body and recently have been stressed by Morgan and Williams.¹¹

From the practical standpoint, a change involving degeneration and increased volume of the orbital tissues is important because the orbit is a closed cavity and the only way for these edematous tissues to gain more space is to push the globe of the eye forward. This, of course, produces exophthalmos and interferes with venous return from the orbit, so that a vicious cycle results with still further

* Studies on the thyrotropic hormone in the urine of patients with exophthalmos are now in progress in collaboration with Dr. Leslie L. Bennett. Hertz and Colver, quoted in reference 14, previously have done similar work in a paper now in preparation.

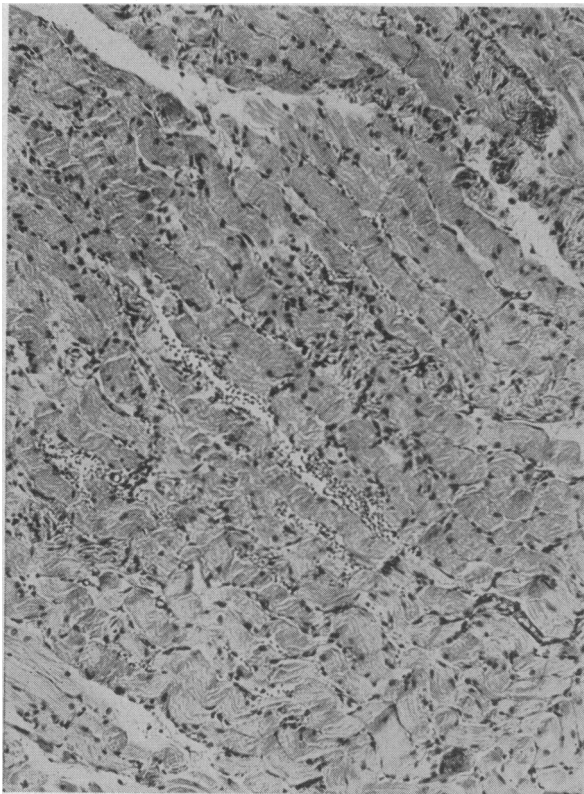


Fig. 3.—Photomicrograph (X120) of section of eye muscle removed during a supraorbital decompression from a 48-year-old Chinese male with severe exophthalmos, bilateral corneal ulceration and infection. Though these eye muscles are not normal, there is surprisingly little edema, cellular infiltration or fibrosis when one considers that his right eye regressed 6 mm. following decompression and his left eye 5 mm. The reaction here is a much more chronic one than that shown in Figures 1 and 2.

edema and proptosis as the end effect. Progressive exophthalmos is that stage in which the process is irreversible and where the nutritional state is such that corneal ulceration and panophthalmitis are common sequelae. In such a state, supraorbital decompression may be life-saving.

One can calculate from average volume measurements of the orbital cavity that an increase of 10 to 20 per cent in the volume of the orbital contents will cause a proptosis of about 1.5 to 3.0 millimeters.* A state of edema that increases the volume of a muscle by 10 per cent or more is not demonstrable by ordinary pathological techniques employed in examination of surgical specimens, a fact that accounts for minimal pathological changes seen in severe exophthalmos (Plate 3).

MEASUREMENTS OF EYES IN PATIENTS WITH VARIOUS TYPES OF GOITER

Several types of instruments are suitable for the measurement of exophthalmos. The Hertel ophthalmometer was used in studying our patients and normal controls. This instrument allows reasonable accuracy after the operator has gained experience by practice. The actual measurement obtained is the distance between the deepest portion of the

lateral wall of the bony orbit and the point of greatest convexity of the cornea. When the instrument is properly placed as described in a previous article,⁴ the error of measurement for the individual trained observer is about one-half to one millimeter.

Using this method, the degree of exophthalmos was determined in 165 patients with toxic diffuse goiters, in 74 patients with toxic nodular goiters, and in 92 patients with nontoxic nodular goiters. The eyes of 65 normal persons were measured as a control series. The patients were subjected to repeated measurements after treatment of their hyperthyroidism to determine changes in the prominence of their eyes.

The results of measurements made before treatment are shown in Table 1. The eyes of normal persons and of those with nontoxic goiters are equally prominent. This finding should be expected since patients with nontoxic goiters should not have exophthalmos unless the goiter is of such size that the venous return from the head is interfered with, and venous pressure in the orbit is raised above normal.

Patients with toxic diffuse goiters have more prominent eyes than normal persons.^{4,12} In a previous report, Soley⁴ found this difference to be a significant one in 106 patients. Since that report, fifty-nine more such patients have been studied, with similar findings (Table 1). Mainini¹² made similar observations, but found fewer patients without measurable exophthalmos. If one concedes that the mechanism of production of exophthalmos is that described above, then variation in edema of the orbital tissues must be expected and, consequently, a variation in the degree of protrusion of the eyeball. This degree of protrusion, in turn, would not cause such evident exophthalmos in a person whose normal measurements were 12 millimeters for each eye as in one whose normal measurements were 18 millimeters. When measurements fall within normal limits, periorbital edema, increased orbital resistance, conjunctival injection and scleral edema aid in deciding whether or not actual exophthalmos is present.

Patients with toxic nodular goiters have more prominent eyes than either normal people or patients with nontoxic nodular goiter, but exophthalmos is not so marked as in patients with toxic

TABLE 1.—Measurements of Eyes* in Normal Persons and Patients with Various Thyroid Diseases Before Treatment.

Subjects	Eye	Number of Subjects	Mean	Range
Normals	Rt. eye	65	15.9	11.5-20.0
	Lt. eye	65	15.9	
Patients with non-toxic nodular goiter	Rt. eye	92	15.8	12.5-22.5
	Lt. eye	92	15.9	12.0-22.5
Patients with toxic diffuse goiter	Rt. eye	165	17.4	11.0-29.0
	Lt. eye	165	17.4	12.0-28.0
Patients with toxic nodular goiter	Rt. eye	74	16.3	9.5-22.5
	Lt. eye	74	16.3	10.0-22.5

* A preliminary study with J. B. de C. M. Saunders indicates that an increase in volume of the orbital contents of 14 per cent will cause a protrusion of about 1.5 millimeters, and of 21 per cent about 3 millimeters.

* All measurements were made with the Hertel Exophthalmometer and were recorded in millimeters to indicate the distance between the deepest portion of the lateral wall of the orbit and the point of greatest convexity of the cornea.

TABLE 2.—*Changes in Exophthalmos After Treatment.*

	Treatment	Number of Patients Followed with Serial Measurements	Increase in Promi- nence of Eyes of 1.5 mm. or More (number of patients)	Decrease in Promi- nence of Eyes of 1.5 mm. or More (number of patients)
Patients with toxic diffuse goiter	Operated (subtotal thyroidectomy)	130	54	6
	X-rayed	23	3	6
Patients with toxic nodular goiter	Operated	49	15	4
Patients with non-toxic nodular goiter	Operated	57	10	0

diffuse goiter. This may be explained by the fact that patients with hyperthyroidism and a nodular goiter usually have had a longer and milder course than those with hyperthyroidism and a hyperplastic goiter without nodules, so that the changes in the orbital tissues are more gradual and better tolerated.⁴ In addition, the patients with toxic nodular goiters tend to be older by eight to ten years than those with toxic diffuse goiters. It is common observation that exophthalmos becomes less frequent as age increases in either group of thyrotoxic patients.

CHANGES IN PROMINENCE OF EYES FOLLOWING TREATMENT

The changes in the prominence of eyes of patients with various thyroid diseases following treatment is of interest both to the patient and to his physician. Table 2 summarizes these data. An increase or decrease of 1.5 millimeters or more was considered significant since the experienced observer measuring exophthalmos with a Hertel ophthalmometer should be able to check his readings within 0.5 to 1.0 millimeter. Many patients had increases of 2.0 to 5.0 millimeters in their exophthalmos, whereas only a few had a decrease of 1.5 millimeters or more.

Of the patients with toxic diffuse goiters who underwent the procedure of subtotal thyroidectomy, 130 were followed sufficiently long (up to seven years) to determine the changes in exophthalmos. Fifty-four, or 41.5 per cent, had a significant increase in exophthalmos, while only six, or 4.6 per cent, had a significant decrease. In the x-ray series of twenty-three patients followed for similar lengths of time, only three, or 13.0 per cent, had a significant progression of their exophthalmos.

The changes in the prominence of the eyes of the patients with toxic nodular goiters were similar, since fifteen, or 30.6 per cent, of forty-nine followed had an increase in exophthalmos, and four, or 8.2 per cent, showed a decrease.

More difficult of explanation is the finding that ten, or 17.5 per cent, of the patients with nontoxic nodular goiters had significant protrusion of their eyes following subtotal thyroidectomy. The orbital tissues of none of these patients have been examined pathologically, so the mechanism of this change is not known. It is conceivable that the anterior lobe of the pituitary gland may play a part and that the immediate cause is again edema and

other cellular alterations in the extraocular muscles and orbital fat.

DISCUSSION

It is surprising that the various instruments used for measuring exophthalmos have not been employed more frequently in patients with thyroid diseases. Series of measurements give us information about the incidence of exophthalmos and the changes in eyes following treatment of the thyroid conditions. For example, it is now apparent that malignant exophthalmos is only extreme progression of exophthalmos, and that moderate progression takes place in 30 to 50 per cent of patients with either toxic diffuse or toxic nodular goiter after subtotal thyroidectomy. Since progression has been shown to be less common in toxic diffuse goiter treated with x-ray,¹³ this type of therapy may be desirable in patients in whom exophthalmos is a presenting symptom.^{4,14} Roentgen therapy is not desirable when the patient has a nodular goiter since a small percentage of the nodules will be neoplastic.^{15,16,17}

Patients whose eyes were more prominent by measurement with an ophthalmometer were, in general, ones whose eyes appeared to be more exophthalmic by clinical observation.⁴ This again points to the fact that good clinical observation is often as important as precise methods of measurement.

The cause of the edema and cellular infiltration in the orbital tissues is not completely solved. These changes can be produced, experimentally, in animals by thyrotropic hormone injections (Aird¹⁰), and are more marked following thyroidectomy (Marine⁸). Edema resulting from hypersecretion of thyrotropic hormone may interfere with the venous return from the orbit and with nutrition of the orbital tissues, which in turn will cause further edema, cellular damage, and progressive exophthalmos. Supraorbital decompression (and this effect may be life-saving) provides greater space for the extraocular muscles and other structures, allowing better venous drainage and permitting the optic nerve to recover normal function and corneal ulcers to heal.

Any cause of edema of orbital tissues may produce exophthalmos which is usually not associated with a stare and, therefore, often not noticed. Such diseases as mediastinal tumors with interference of venous drainage from the head, nephritis¹⁸ and myxedema¹² should be included in this group. We have had several patients with myxedema whose

eyes regressed 1.5 to 2.0 millimeters after adequate substitution therapy with thyroid.

Although the exophthalmos discussed in this paper is limited to that seen in thyroid diseases, it must be remembered that there are many other diseases associated with proptosis of the eyeball. These may be listed briefly as follows: sinusitis, intracranial arteriovenous aneurysms, benign or malignant tumors (either primary or metastatic) of the orbit or skull, thrombosis of the cavernous sinus, xanthamatoses, congenital malformation of the skull, Paget's disease, hypertension, nephritis, gumma of the orbit, and voluntary exophthalmos. We have learned from experience that patients with severe exophthalmos require more frequent clinical observation to prevent, if possible, progression of exophthalmos. We feel that radical subtotal thyroidectomy is not indicated, but if thyroidectomy must be carried out because of the large size of the goiter or because it is nodular, more thyroid tissue should be left *in situ* than is customary. Routinely, our surgeons leave 3 to 4 grams; in this special group of exophthalmic patients, 5 to 7 grams should be left in order that no patient will go through a phase of hypothyroidism during the period of six to twelve weeks postoperatively. If hypothyroidism complicates the patient's convalescence, thyroid should be administered in a dosage that precludes any possibility of myxedematous changes in the orbital tissues. Usually, serum protein levels can be kept normal with adequate protein intake, thus eliminating another possible cause of edema.

Empirically, we have found that patients with symptoms of lacrimation and photophobia are relieved in part with large doses of vitamin A (50,000 to 75,000 units) daily. Biophotometer tests and low blood levels of vitamin A and carotene indicated vitamin A deficiency in some of these patients.

SUMMARY

Normal persons and patients with nontoxic nodular goiters have equally prominent eyes. Patients with toxic diffuse goiters have significantly more prominent eyes than normal persons. Patients with toxic nodular goiters in general have less prominent eyes than those with toxic diffuse goiters.

About 40 per cent of patients with toxic diffuse goiters have progression of exophthalmos following subtotal thyroidectomy, while only about 5 per cent have regression. A much smaller percentage (13 per cent) of our series of patients treated with roentgen rays had a significant increase in prominence of their eyes. Of fifty-seven patients with nontoxic nodular goiters, 17 per cent had a significant increase in the prominence of their eyes following subtotal thyroidectomy.

Exophthalmos associated with toxic goiters is produced by edema, cellular infiltration, and sometimes fibrosis of the extraocular muscles, and edema of other orbital tissues. These tissue changes in such patients may be caused by hyperactivity of the anterior lobe of the pituitary gland, particularly hypersecretion of the thyrotropic hormone.

A staring expression should be differentiated from true exophthalmos. Exophthalmos may be recognized by actual prominence of the globe and by coincidental signs such as conjunctivitis, peri-orbital and scleral edema, excessive lacrimation, abnormal function of the extraocular muscles and increased orbital resistance. Exophthalmos may be confirmed by measurement of the prominence of the eyes by an ophthalmometer.

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